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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/837,217	04/19/2001	Chia Ning (Sophia) Chang	01779784	6921

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/837,217	CHANG, CHIA NING (SOPHIA)	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8 and 11-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8 and 11-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/03 has been entered.

Amended claims 1-6, 8 and new claims 11-14 are pending in the present application.

New Matter

Amended claims 1-4 and new claims 11, 13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 recites "comprising a plurality of bone marrow stromal cells (MSCs) isolated from the subject; wherein the MSCs comprise a vector comprising a DNA sequence encoding BMP-2 operably linked to a promoter". There is no literal support in the originally filed specification for Applicant's contemplation specifically for the preparation of a pharmaceutical composition comprising a plurality of MSCs which were isolated from a subject and wherein said MSCs comprise a DNA sequence encoding

BMP-2 operably linked to a promoter. While the specification teaches in general for a harvest of bone marrow stromal cells from a subject, followed by a adenovirus BMP-2 transduction of the isolated bone marrow stromal cells *in vitro* (page 5, Summary of the Invention and examples), there is no literal written support that Applicant contemplates specifically for the isolation of bone marrow stromal cells that already comprise a vector comprising a DNA sequence encoding BMP-2 operably linked to a promoter from a subject for the preparation of a pharmaceutical composition as claimed. Applicant failed to specifically point out specific page numbers and/or line numbers in the present application that provide literal supports for the aforementioned amendment. Therefore, given the lack of written support in regarding to the aforementioned issue from the originally filed specification, it would appear that Applicant did not have possession of the claimed invention at the time the application was filed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 1-6, 8 and 11-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of enhancing new bone formation in a subject, comprising:

a) obtaining a plurality of bone marrow stromal cells (MSCs) from the subject;

b) transducing the MSCs of step a) with a replication-defective adenovirus vector comprising a DNA sequence encoding BMP-2 operably linked to a promoter to generate BMP-2 protein producing MSCs;

c) applying a biodegradable plate to a site requiring new bone formation on the subject; and

c) applying a composition comprising the BMP-2 protein producing MSCs and a pharmaceutically acceptable polymer to the site,

such that new bone formation is enhanced;

does not reasonably provide enablement for a method of enhancing new bone, cartilage or connective tissue formation in a subject using a plurality of bone marrow stromal cells isolated from any subject, and wherein said bone marrow stromal cells are transduced *in vitro* with any vector (both viral and non-viral vectors as well as replication competent and replication-defective viral vectors) expressing BMP-2; or a pharmaceutical composition comprising a plurality of bone marrow stromal cells (MSCs) isolated from a subject, wherein the MSCs comprise a vector expressing BMP-2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. **This is a new ground of rejection.**

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte*

Forman, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The specification teaches by exemplification showing the preparation of autologous bone marrow stromal cells (MSCs) from iliac crests of mini pigs, which are transfected with a recombinant replication-defective adenovirus expressing human BMP-2 (MSCs transfected with adv-BMP-2). In an experimental model of mini-pigs having critical size cranial bone defects, upon implantation of the autologous transfected MSCs in the polymer Pancogene S (collagen type I) at the bone defective site, a significant increase of bone formation was observed at 3 months, indicating that the polymer Pancogene S/MSCs transfected with adv-BMP-2 can enhance the bony healing of critical size craniofacial defect. Similarly, a near-complete defect repair at the defective maxillary bone sites was achieved 3 months after implantation of the autologous transfected MSCs in the polymer Pancogene S at the generated defective sites in minipigs. The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention for the following reasons.

(1) The breadth of the claims. With respect to claims 1-4, 11 and 13, they encompass a pharmaceutical composition for application at a biodegradable plate-containing site requiring new bone, cartilage or connective tissue (e.g., muscle, adipose and other fibrous tissues) in a subject comprising a plurality of bone stromal cells (MSCs) isolated from the subject, wherein the MSCs comprise a vector comprising any vector comprising a DNA sequence encoding BMP-2 operably linked to a promoter, and

a pharmaceutically acceptable polymer. With respect to claims 5-6, 8, 12 and 14, they encompass a method of enhancing new bone, cartilage or connective tissue (e.g., muscle, adipose and other fibrous tissues) in a subject using a plurality of bone marrow stromal cells (MSCs) isolated from a subject (not necessarily limited from the subject in need of enhanced new bone, cartilage or connective tissue formation), and wherein the MSCs are transduced *in vitro* with any vector (both viral and non-viral vectors as well as replication competent and replication-defective viral vectors) expressing BMP-2 protein.

(2) The state and the unpredictability of the prior art. The nature of the instant claims falls within the realm of gene therapy, specifically *ex vivo* gene therapy. At about the filing date of the present application, the attainment of therapeutic effects (for this instance, enhanced formation of new bone, cartilage, muscle, adipose tissue and other fibrous tissues) via gene therapy still remains unpredictable. Romano et al. (Stem Cells 18:19-39, 2000) states "The potential therapeutic applications of gene transfer technology are enormous. However, the effectiveness of gene therapy programs is still questioned....[d]espite the latest significant achievements reported in vector design, it is not possible to predict to what extent gene therapeutic interventions will be effective in patients, and in what time frame" (see abstract). Several factors that are known to limit an effective human gene therapy, and these include suboptimal vectors, the lack of a stable *in vivo* transgene expression, as well as an adverse host immunological responses against delivered recombinant vectors or genetically modified cells, particularly non-autologous cells or xenogeneic cells. The prior art at the fling date of the present application does not teach or provide any guidance for a skilled

artisan on how to make and/or use genetically modified bone marrow stromal cells expressing BMP-2 isolated from any subject, nor does it teach the enhanced formation of new cartilage, muscle, adipose and other fibrous tissues in a subject using autologous bone marrow stromal cells transduced with replication-defective adenovirus expressing BMP-2, let alone any bone marrow stromal cells transduced with any vector expressing BMP-2, as evidenced by the teachings of Riew et al. (Calcif. Tissue Int. 63:367-360, 1998; Cited previously), Cheng et al. (Calcif. Tissue Int. 68:87-94, 2001; Cited previously), Lou et al. (J. Orthopaedic Research 17:43-50, 1999; Cited previously), and Moutsatsos et al. (WO 99/11664, Cited previously).

(3) The amount of direction or guidance provided. Apart from the exemplification showing that a significant and enhanced bone formation occurs at a bony defective site using autologous MSCs transfected with a recombinant replication-defective adenovirus expressing human BMP-2, the instant specification fails to provide sufficient guidance for a skilled artisan on how to repair a defect or injury at any non-bony tissues, e.g., cartilage, muscle, adipose or other fibrous tissues. There is no evidence of record indicating or suggesting that the exogenous expression of BMP-2 in MSCs could induce any transfected bone marrow stromal cells to differentiate into cells that result in enhanced cartilage, muscle, adipose or other fibrous tissues *in vivo*. Furthermore, Lou et al. (J. Orthopaedic Research 17:43-50, 1999) and Cheng et al. (Calcif. Tissue Int. 68:87-94, 2001) already teach that adenovirus-mediated human BMP-2 gene transfer induces mesenchymal progenitor C3H/10T cells and mesenchymal stem cells to proliferate and differentiate into osteoblast phenotype that

result only in induced bone formation *in vitro* and *in vivo* (see abstract). The instant specification also does not provide any guidance for a skilled artisan on how to obtain any genetically modified bone marrow stromal cells expressing BMP-2 protein from any subject (e.g., the source and/or how to prepare such genetically modified subject) for the preparation of a pharmaceutical composition as claimed. Additionally, it is unclear whether other vectors apart from the exemplified recombinant replication-defective adenovirus are efficient to transduce isolated bone marrow stromal cells and/or to establish an effective BMP-2 level *in vivo* to induce or enhance new bone formation *in vivo*, let alone new cartilage or other connective tissues. A number of obstacles that have severely limited the application of nonviral-based vectors in therapy, include the low transfection efficency, the transient transgene expression, a strong and adverse host immune responses against CpG islands present in bacterial DNA (Romano et al., see page 30, top of first full paragraph). Moreover, it is also uncertain about the effects of other recombinant vectors on the differentiation and/or proliferation of bone marrow stromal cells *in vivo* to yield the desired therapeutic effects contemplated by Applicants. It should be further noted that the ultimate fate of an undifferentiated stem cell is determined by local growth factors (for this instance the effective exogenous BMP-2 level *in vivo*) and by the environment to which the mesenchymal stem cell (present in bone marrow stromal cells) is exposed.

Since the prior art at the filing date of the present application does not provide guidance on the aforementioned issues, it is incumbent upon the instant specification to do so. In the absence of sufficient guidance provided by the present application, it

would have required undue experimentation for one skilled in the art to make and use the presently claimed invention. As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

(4) Working examples. There is no example for how to make and/or use any bone marrow stromal cells (MSCs) comprising a vector comprising a DNA sequence encoding BMP-2 isolated from any subject. Nor is there any example for enhancing new cartilage or other connective tissue formation in a subject using any bone marrow stromal cells tranduced with any vector comprising a DNA sequence encoding BMP-2 protein, let alone using non-autologous bone marrow stromal cells genetically modified with any non-adenoviral vectors expressing BMP-2 protein.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the gene therapy art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Response to Arguments

Applicant's arguments related to the issue on the formation of new cartilage or connective tissue by the presently claimed invention in the above rejection in the

Amendment filed 03/05//03 have been fully considered, but they are not found persuasive.

Applicant argues basically that at the time of Applicant's invention the expression of BMP-2 in pluripotent stem cells (such as bone marrow stromal cells) can induce the cells to differentiate into cell types other than osteoblasts, e.g., cartilage and connective tissue, as evidenced by the teachings of Moutsatsos et al. (WO 99/11664) on page 8, lines 16-22 and page 9, lines 5-12. Therefore, the ordinary skilled artisan would be able to enhance the formation of cartilage or connective tissue as well as bone without undue experimentation.

The examiner notes that example 1 (pages 7-9) is the only example in which transplants of C.9 cells (C3H10T1/2 cells transduced with a recombinant retrovirus encoding β-galactosidase and a vector (it is not clear which vectors) expressing BMP-2 under the control of a Tet inducible promoter) developed into newly formed ectopic bone and cartilage in muscles of –Dox animals (please also note no formation of muscle, adipose or other connective tissues). The C.9 transplant is not the same as a composition comprising genetically modified bone marrow stromal cells of the presently claimed invention. Furthermore, subsequent examples of Moutsatsos et al. only showed the formation of newly ectopic bone *in vivo* (example 2, pages 9-10, example 11, pages 24-26). Additionally, the exemplification of the present disclosure as well as the teachings of Riew et al. (Calcif. Tissue Int. 63:367-360, 1998), Lou et al. (J. Orthopaedic Research 17:43-50, 1999), and Cheng et al. (Calcif. Tissue Int. 68:87-94, 2001) demonstrate that adenovirus-mediated human BMP-2 gene transfer induces

mesenchymal progenitor C3H/10T cells and mesenchymal stem cells to proliferate and differentiate into osteoblast phenotype that result only in induced bone formation *in vivo*. Thus, in light of the totality of the prior art at the filing date of the present application, it would have required undue experimentation for a skilled artisan to make and use the instant broadly claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Amended claims 1-2, 11 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Moutsatsos et al. (WO 99/11664) for the same reasons already set forth in the previous Office Action mailed 5/13/03 (pages 3-4).

Amended claims 1-2, 4, 11 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Riew et al. (Calcif. Tissue Int. 63:357-360, 1998) as evidenced by Caplan et al. (U.S. 5,855,619) for the same reasons already set forth in the previous Office Action mailed 5/13/03 (pages 4-5).

Amended claims 1-2, 4, 11 and 13 are rejected under 35 U.S.C. 102(a) as being anticipated by Cheng et al. (Calcif. Tissue Int. 68:87-94, 2001) as evidenced by Caplan et al. (U.S. Patent No. 5,855,619) for the same reasons already set forth in the previous Office Action mailed 5/13/03 (pages 5-6).

The examiner would like to note that the compositions taught by Moutsatsos et al. (WO 99/11664), Riew et al. (Calcifi. Tissue Int. 63:357-360, 1998) and Cheng et al. (Calcif. Tissue Int. 68:87-94, 2004) are indistinguishable from the pharmaceutical composition as claimed. It should be noted that the presently claimed composition only requires a plurality of bone marrow stromal cells isolated from a subject, wherein the MSCs comprise a vector comprising a DNA sequence encoding BMP-2 operably linked to a promoter, and a pharmaceutically acceptable polymer.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER